REMARKS

Claims 1, 17-19, 23, 29, 34-38, 44, 47, and 54-63 are pending in this application. All of the claims are rejected under 35 U.S.C. § 103(a) for obviousness. Claims 19, 29, 34-36, 47, and 54-63 also stand rejected under 35 U.S.C. § 112, second paragraph. Claims 1, 17-19, 23, 29, 34-38, and 56-60 also stand rejected under the judicially created doctrine of obviousness-type double patenting. Each of the Office's rejections is addressed below. Applicants respectfully request reconsideration of the claims as amended.

Support for the Amendments

Claims 1, 17-19, 23, 29, 34-38, 47, and 56-60 have been cancelled. Claim 44 has been amended to independent form. Claims 54 and 55 have been amended to depend from claim 44 and to recite the limitation that the human constant region is IgG, IgA, or IgM (claim 54) or IgG1 (claim 55). Claim 57 has been amended to depend from claim 44. Claim 61 has been amended to independent form. Claims 62 and 63 have been amended to depend from claim 61 and to recite the limitation that the human constant region is IgG, IgA, or IgM (claim 62) or IgG1 (claim 63). Support for these amendments is found throughout the specification and the claims, for example, in previously pending claims 17, 18, 34-36, 54-55, 58-60, and 62-63. New claim 64, which depends from claim 57, has been added. This claim recites the limitation that the pharmaceutical composition further includes a pharmaceutically acceptable carrier or diluent. Support for this claim is found throughout the specification and the claims, for example, in previously pending claims 23, 29, and 57. No new matter is added by these amendments.

Applicants note that the cancellation, abandonment, or amendment of any claim or any amendment of the description does not amount to abandonment of any subject matter in the application, and Applicants reserve the right to pursue some or all of such subject matter in this application, or in one or more divisional applications. Additionally,

Applicants reserve the right to file divisional applications in respect of any subject matter in the application as filed.

Objections to the Claims

The Office objects to claim 1 for referencing the figures and the use of parenthesis. Applicants have cancelled claim 1 rendering the objection moot.

Rejections under 35 U.S.C. §103(a)

Claims 1, 17-19, 23, 29, 34-38, 44, 47, and 54-63 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Speirs et al. (*Canadian Journal of Microbiology*, 37:650-653, 1991; "Speirs") or O'Brien et al. (U.S. Patent No. 5,747,272; "O'Brien") in view of Carter et al. (WO 94/04679; "Carter") or Shitara et al. (U.S. Patent No. 5,866,692; "Shitara") and further in view of Tzipori et al. (U.S. Patent Application Publication No. 2003/0082189; "Tzipori"). Speirs and O'Brien are cited for disclosing the mouse 13C4 and 11E10 antibodies. Carter and Shitara are relied upon for disclosing methods of producing humanized antibodies. Tzipori is cited for disclosing that monoclonal antibodies specific for Shiga toxins can be used to treat hemolytic uremic syndrome. The Office maintains the rejection on the basis that it would have been obvious for a skilled artisan to employ the methodologies disclosed by Carter to humanize the 13C4 and 11E10 antibodies and that the motivation to do so is provided by Tzipori. Applicants respectfully traverse the rejection as it applies to the current claims.

Applicants' invention features pharmaceutical compositions that include a humanized monoclonal antibody that specifically binds to Stx1 and a humanized monoclonal antibody that specifically binds to Stx2. All of the claimed antibodies feature a human immunoglobulin constant region and a defined murine variable region. The defined murine variable regions consist of variable region sequences provided as either the SEQ ID NOs for the heavy and light chain variable regions or by the ATCC deposit

number of the anti-Stx1 or anti-Stx2 murine antibody. Applicants submit that there is nothing in the references of record that provides a basis for humanizing the 13C4 and the 11E10 antibodies, each directed against a distinct Shiga toxin and then combining the humanized antibodies to arrive at the pharmaceutical composition as presently claimed.

Speirs and O'Brien describe using the mouse 13C4 and 11E10 antibodies in a diagnostic kit for detecting Shiga-like toxins. There is nothing in Speirs or O'Brien that teaches, suggests, or motivates the skilled worker to humanize each of the antibodies of Speirs and O'Brien and to then combine both antibodies in a pharmaceutical composition. The description of a use of the 13C4 or 11E10 antibodies in an *in vitro* diagnostic kit does not teach or suggest that these same antibodies would be effective combined together in a pharmaceutical composition.

Carter and Shitara describe general methods for humanizing an antibody, and each fails to describe or mention either the 13C4 or 11E10 antibody, let alone a composition that includes both humanized antibodies.

The Office states that Tzipori provided the necessary motivation to humanize the antibodies "in order to use them in the treatment methodologies disclosed." Tzipori, however, fails to provide motivation to produce a composition that includes both humanized 13C4 and 11E10 antibodies because Tzipori describes completely different antibodies and fails to even mention 13C4 or 11E10. As detailed in Applicants' previous response filed on October 30, 2007, Tzipori chose to use completely different antibodies for the treatment of hemolytic uremic syndrome despite the fact that at the time Tzipori's priority application was filed, the 13C4 and 11E10 mouse monoclonal antibodies had been known in the art as diagnostic reagents for *over five years* (Speirs was published in August of 1991 and Tzipori's priority application was filed on November 15, 1996). Applicants submit that a skilled artisan, upon reading Tzipori, would not be motivated to choose two separate antibodies that Tzipori himself chose not to use, to humanize those antibodies, and to combine the antibodies in a pharmaceutical composition in order to

arrive at the presently claimed pharmaceutical composition. In response to Applicants' previous arguments, the Office reminds Applicants that "one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references." Applicants are well aware of this point but submit that the Office has specifically cited Tzipori for providing the motivation to humanize the antibodies (see, for example, the top of page 9 of the present Office action) and Applicants arguments are directed to this aspect of the rejection.

Applicants further submit that the Office has not established a *prima facie* case of obviousness specific to the compositions having both humanized antibodies despite the fact that these claims were previously pending, albeit in a dependent format. Instead, the Office's position relies solely on the fact that, according to the Office, it would have been obvious to humanize the mouse 13C4 and 11E10 antibodies. In view of the arguments presented above and the absence of a factually supported *prima facie* case of obviousness specific to the pharmaceutical composition claims, Applicants submit that the present claims are not obvious over the cited prior art documents. Applicants respectfully request that the rejection under § 103 for obviousness, as it pertains to the current claims, be withdrawn.

Rejections under the Judicially Created Doctrine of Obviousness-Type Double Patenting

The Office has maintained the rejection of claims 1, 17-19, 23, 29, 34-38, and 56-60 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 9 of U.S. Patent No. 5,747,272 ("the '272 patent") in view of Carter et al. (WO 94/04679; "Carter"). By way of the present amendment, Applicants have cancelled claims 1, 17-19, 23, 29, 34-38, and 56-60 rendering the rejection, as it applies to these claims, moot.

Claims 1, 17-18, 23, 37, and 56-60 stand provisionally rejected for nonstatutory obviousness-type double patenting over claims 25-36 and 38 of copending application

U.S.S.N. 11/788,546. All rejected claims have been cancelled rendering the rejection moot.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 19, 29, 34-36, 47, and 54-63 stand rejected under 35 U.S.C. § 112, second paragraph on the basis that the term "said variable region consists of the murine X (ATCC Accession No. X) variable region" is vague and indefinite. While not agreeing with the Office, for clarity, Applicants have amended claim 61 to recite the limitation that the antibody comprises a variable region that consists of the murine 13C4 or 11E10 (ATCC Accession No. provided) heavy chain and light chain variable regions. Claims 62-63 depend from claim 61 and, by definition, include all limitations of claim 61. The remaining rejected claims have been cancelled. In view of this amendment, Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

Applicants submit that the pending claims are in condition for allowance and such action is respectfully requested.

Enclosed are a Petition to extend the period for replying to the Office Action for five months from the date of receipt of the Notice of Appeal, to and including March 15, 2009, and a check in payment of the required extension fee.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: March 11, 2009

James D. DeCamp, Ph.D.
Reg. No. 43,580

for Kimya F. Harris, Ph.D.
Reg. No. 57,172

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045